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US system of oversight for genetic testing: a report from the Secretary's Advisory Committee on Genetics, Health and Society

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Abstract

As genetic testing technology is integrated into healthcare, increasingly detailed information about individual and population genetic variation is available to patients and providers. Health professionals use genetic testing to diagnose or assess the risk of disease in individuals, families and populations and to guide healthcare decisions. Consumers are beginning to explore personalized genomic services in an effort to learn more about their risk for common diseases. Scientific and technological advances in genetic testing, as with any newly introduced medical technology, present certain challenges to existing frameworks of oversight. In addition, the growing use of genetic testing will require a significant investment in evidence-based assessments to understand the validity and utility of these tests in clinical and personal decisionmaking. To optimize the use of genetic testing in healthcare, all sectors of the oversight system need to be strengthened and yet remain flexible in order to adapt to advances that will inevitably increase the range of genetic tests and methodologies.

Keywords

analytical validity; CLIA; clinical decision support; clinical utility; clinical validity; genetic testing; health communication; oversight; proficiency testing; US FDA

In March 2007, the US Department of Health and Human Services (HHS) launched the Personalized Health Care (PHC) Initiative to advance the integration of genomic technologies that are capable of tailoring treatment and prevention strategies to each patient's unique genetic characteristics and individual needs into general healthcare [101]. The expanded use of genetic testing in clinical practice and public health, and the pace and extent of technological change in testing, have prompted efforts to examine the current system of oversight of genetic tests and test results. Consequently, the HHS Secretary charged the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) with investigating specific issues related to the adequacy and transparency of the current US oversight system for genetic testing. SACGHS, chartered in 2002, is a public forum for the deliberation of policy issues raised by the

development and use of genetic tests and, as warranted, to provide advice to the HHS Secretary on these issues [102].

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Answering the charge

The HHS Secretary asked SACGHS to assess the adequacy of information regarding analytic validity, clinical validity and clinical utility of genetic tests (see definitions in Box 1) and the organizations responsible for oversight. The charge also questioned the availability of proficiency testing (PT) for genetic tests and communication aides to guide test selection and interpretation of results. In particular, the Secretary was interested in current gaps in oversight and how enhanced oversight would improve health outcomes and reduce harms.

To respond to the charge, SACGHS members and representatives from federal agencies – with the help of invited experts [103] – conducted extensive reviews of the literature, analyzed prior policy recommendations and reviewed current policies and relevant activities of federal and state agencies and private sector organizations. The Committee used a broad interpretation of oversight that included federal and state governments and agencies, standard-setting organizations, knowledge-generating organizations, public and private sector healthcare payers, professional societies, health providers, patients and consumers. As there is no standard accepted definition of genetic or genomic test, the definition in Box 1 was used for the purposes of the oversight report.

A draft report was released for public comment, and the report was revised based on these comments. In February 2008, SACGHS approved final recommendations that address gaps in the oversight of genetic testing, and the final report [104] was submitted to the HHS Secretary in April 2008. Although SACGHS was tasked to look at the oversight of genetic testing specifically, it found that the issues associated with genetic tests do not differ markedly from other complex laboratory tests (i.e., genetic tests are not unique or exceptional for oversight purposes). Therefore, the Committee's recommendations could be applied more broadly to improve the quality and oversight of all laboratory tests.

Definition of key terms

- Analytical validity is the ability of a test to measure a particular genetic characteristic (e.g., a DNA sequence) accurately and reliably in a given specimen.
- Clinical validity of a genetic test refers to the test's accuracy in detecting the presence of, or predicting the risk for, a health condition or phenotype.
- Clinical utility represents a balance between health-related benefits and the harms that can ensue from a genetic test.
- Genetic or genomic tests, as defined in the Secretary's Advisory Committee on Genetics, Health and Society report, involve an analysis of human chromosomes, DNA, RNA, genes and/or gene products (e.g., enzymes and other types of proteins), and are predominately used to detect heritable or somatic mutations, genotypes or phenotypes related to disease and health. The purpose of genetic tests includes predicting risk of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families or populations. Excluded from the definition are tests conducted exclusively for forensic and identity purposes, and tests conducted purely for research. Also excluded are tests that are used primarily for other purposes but may contribute to diagnosing a genetic disease or disorder (e.g., blood smears, certain serum chemistries). For example, cholesterol screening in the general population is not considered a genetic test, but it may reveal a genetic disorder such as an inherited form of hypercholesterolemia.

- Nonwaived laboratory tests are moderate and high complexity laboratory examinations and procedures that pose a significant risk if there is an erroneous result. Under Clinical Laboratory Improvement Amendments (CLIA) regulations, US FDA categorizes laboratory tests as waived or nonwaived (with moderate or high complexity) [113].
- Pharmacogenomic testing analyzes whole genomes or specific candidate genes or biomarkers for alterations in gene expression affecting drug action or activity.

Key players in the US oversight system for genetic testing

The US oversight system for genetic testing addresses activities that range from the research and development of tests to the delivery and interpretation of tests results that guide health and lifestyle decisions. Some aspects of oversight are quite specific to genetic testing, while others apply more broadly to the healthcare system. At the US federal level, oversight of genetic tests is carried out primarily by the US FDA and the Centers for Medicare and Medicaid Services (CMS). Other federal agencies play a role in establishing standards, developing practice guidelines and assessing false or misleading advertising. Other key stakeholders are state-level regulatory agencies, payers, health professional societies, industry organizations, private-sector accreditation bodies, patient advocacy groups and consumers. Table 1 summarizes some of the elements of the oversight framework for genetic testing.

Currently, in the USA, there are two main pathways to make genetic tests available for clinical use. Some genetic tests are developed as products by *in vitro* diagnostic test manufacturers for commercial distribution to multiple laboratories; these tests are regulated by the FDA [105]. Other tests, known as laboratory-developed tests (LDTs), are for use solely within the developer's laboratory and are not sold to other entities, but are offered as professional services to patients and clinicians. Currently, most of the available genetic tests are LDTs. Laboratories that develop LDTs are regulated by requirements of the Clinical Laboratory Improvement Amendments (CLIA) of 1988 [106]. CLIA regulations, which are overseen by CMS, require all clinical laboratories that perform nonwaived tests (see definition in Box 1) to undergo biennial inspections to assess their compliance with established standards.

The use of genetic tests may also be regulated at the state level. A complex web of state statutes, regulations and liability rules guides their use. State medical practice acts, informed consent statutes, laboratory standards, state genetic testing statutes and privacy acts, and state tort liability rules serve to define the physician's standard of care. State-level laws, such as those for newborn screening, affect whom to test, when to test and which test to use.

In addition to governmental agencies, many groups, such as professional societies and industry organizations, play a role in oversight through various activities such as accreditation of laboratories, standards development, advancement of best laboratory practices, sponsorship of PT programs, development of clinical guidelines and promotion of health professional and patient education in human genetics.

Key findings

SACGHS identified gaps in five main areas of oversight that directly affect the optimal use of genetic testing:

- Clinical laboratory quality assurance
- Transparency of genetic testing
- Oversight of the clinical validity of genetic tests

- Level of current knowledge regarding clinical utility of genetic tests
- Meeting the informational needs of health professionals, the public health community, patients and consumers.

Gaps in clinical laboratory quality assurance affect the accuracy of test performance. The Committee was particularly concerned with inadequacies in CLIA requirements for PT and the limited availability of reference materials from PT providers for assay, analyte and platform validation. It also agreed with the CMS analysis that new and continual training is needed for personnel who conduct CLIA inspections of laboratories performing genetic tests.

Complete information on the number, types and validity of genetic tests offered in clinical and public health practice is not directly available to the public in a centralized repository. Manufacturers of commercial genetic test products must register with the FDA, but developers of LDTs do not. This gap leads to a lack of transparency and insufficient information about genetic tests that is directly accessible by the public, such as test availability; PT or other performance assessment data; and measures of analytical validity, clinical validity and clinical utility.

The optimal use of genetic testing is challenged by incomplete data on clinical validity and clinical utility for many genetic tests and inadequate processes for conducting such assessments. There are missed opportunities to collect post-market outcome data to assess clinical validity and utility and the impact of genetic testing – including direct-to-consumer testing – on patient care and public health. In addition, there has been limited monitoring of and enforcement against laboratories and companies that make false and misleading claims about genetic tests [1].

Deficiencies in the genetic knowledge of practitioners, public health workers, patients and consumers hamper interpretation and communication of genetic test results. Improvements in tools such as interoperable electronic health records (EHRs) are needed to support the use of practice guidelines and clinical decision support tools.

SACGHS recommendations to enhance the oversight of genetic testing

To address gaps in oversight, the Committee made 15 recommendations and emphasized the importance of enforcing existing regulations and promoting new partnerships between the federal government and the private sector. Table 2 provides a brief summary of recommended actions, and the following discussion highlights the Committee's main recommendations. A full discussion is available in the SACGHS oversight report [104].

In considering gaps in laboratory quality assurance, it is important to recall that SACGHS concluded that genetic tests do not differ markedly from other complex laboratory tests for the purposes of oversight. The Committee therefore recommended that CMS require PT of all nonwaived laboratory tests for which PT products are available. To promote the development of new PT products and novel performance assessment efforts, HHS should fund studies of the effectiveness of alternative performance assessment methods to determine whether they are as robust as PT, and also fund development of reference materials and methods. SACGHS also recommended that experts be used to train CLIA laboratory inspectors in the practical application of CLIA requirements. In addition, HHS should explore mechanisms for developing new authorities and resources that will enable CMS to strengthen its enforcement efforts against laboratories that perform genetic tests for clinical purposes without proper CLIA certification.

To better understand the types of genetic tests currently being offered and facilitate the oversight of laboratory tests, SACGHS recommended that HHS appoint and fund a lead agency

to develop and maintain a mandatory, publicly available, web-based registry for laboratory tests. A web-based registry should provide information regarding the availability of testing, analytical validity, clinical validity and, where available, clinical utility of laboratory tests. While awaiting implementation of a mandatory registry, HHS should use short-term voluntary approaches such as incentivizing laboratories to register with GeneTests [107], and encouraging laboratories to make their test menus and analytical and clinical validity data for these tests directly available to the public.

The Secretary's Advisory Committee on Genetics, Health and Society recommended that the FDA take action to help close the gaps in oversight related to clinical validity, which would help to assure the appropriate use of laboratory tests. In this recommendation, the Committee calls for the FDA to assess all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or a LDT), in a manner that takes advantage of its current risk-based regulatory approach. In addition, the FDA and the Federal Trade Commission should strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about genetic tests, especially those offered directly to consumers.

The Committee also recommended research and programmatic efforts to close the extensive gaps in knowledge regarding the clinical utility of genetic tests and the impact of genetic testing on patient care. Specifically, HHS should create and fund a public/private entity to assess the clinical utility of genetic tests and develop a research agenda to address gaps in knowledge. These efforts should build on an initiative known as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) [108], which is within the Centers for Disease Control and Prevention. HHS should also conduct public health surveillance to assess health outcomes (or appropriate surrogate outcomes) and the impact of genetic testing. As EHRs will serve as a critical resource for assessing the clinical utility and value of genetic testing, HHS should ensure the coordination of groups addressing standards for EHRs, personalized healthcare, population health, confidentiality, privacy and security.

Meeting the varied genetics informational needs of health professionals, public health workers, patients and consumers deeply concerned the SACGHS. Therefore, the Committee recommended that the HHS support efforts to identify education or training deficiencies in each of these groups and support research and development of effective resources such as clinical decision support and point-of-care education systems. These efforts should take into account differences in language, culture, ethnicity and perspectives on health and disability, as well as issues of medical literacy, access to electronic information sources such as the internet, and deficiencies in public infrastructures (e.g., libraries) that can affect the use and understanding of genetic information. Owing to the importance of clinical decision support systems in the pre- and post-analytical periods of laboratory testing, clarification of the nature and scope of FDA oversight of these systems is critical. In light of the changing healthcare delivery and healthcare data collection systems, the SACGHS recommended that the FDA gather perspectives from all interested stakeholders on the appropriate regulatory framework for clinical decision support systems. The FDA should then prepare a guidance document articulating the scope of its regulation of clinical decision support systems.

The SACGHS recommendations provide a roadmap of necessary changes to the US oversight system to maximize the benefits and minimize the harms of genetic testing.

Conclusion

The SACGHS report highlights the complexity of the US oversight system and urges the coordination of activities associated with the oversight of genetic testing, including policy and resource development, education, regulation and knowledge generation. The Committee's

recommendations emphasize the importance of enforcing existing regulations and promoting new partnerships between the federal government and the private sector. The SACGHS believes that its report and recommendations will be helpful in maximizing the benefits of genetic testing and the important role that these tests will play in achieving effective, affordable personalized healthcare.

Future perspective

The US system of oversight for laboratory testing has evolved over several decades in response to many factors, such as the expanding range of tests and services, and a patchwork history of legislation and regulation. Oversight will become more complex with the explosion of genetic technologies, the need for quality assurance, the need for information regarding clinical validity and utility, the demand for testing before adequate information about clinical validity and utility accrues, and the ability of patients and professionals to use the information wisely. Concerns regarding gaps in oversight extend beyond the US borders and solutions would be enhanced by international collaboration.

The ongoing work of certain groups has already begun to address some of the gaps identified in the SACGHS report. For example, the EGAPP and the PHC Workgroup of the American Health Information Community [109] are examining the clinical utility data and information standards for many genetic tests. The National Coalition for Health Professional Education in Genetics [110] and various professional societies support the genetics education and training needs of health professionals by developing point-of-care educational tools and guidelines. CMS has begun to address training needs of personnel who conduct CLIA inspections. However, much additional work will be required to implement the recommendations presented in the SACGHS report.

The diverse uses of laboratory tests, including genetic tests, present different risks, benefits and oversight challenges, which will require substantially different regulatory approaches and oversight mechanisms. Therefore, a ‘one-size-fits-all’ oversight framework for all laboratory tests may not be appropriate. The USA should continue to move towards a framework of ‘tailored oversight’ that applies variable regulatory requirements and oversight mechanisms to different subclasses of laboratory tests. Implementing a tailored oversight approach to the oversight of genetic testing implies the need for risk stratification to determine which tests require which level of oversight. It will be a major challenge to develop a stratification algorithm that will have a compact set of sorting criteria yet also yield consistent results, so that similarly situated tests receive consistent approaches to regulation and oversight. Another key challenge will be the design of a flexible oversight framework that acknowledges the health information technologies of today but can also adapt as new technologies emerge. This framework must strike a balance that lets potentially beneficial new tests move into clinical use, while managing uncertainties until their clinical utility is resolved.

Executive summary

Answering the charge

- The US Secretary of Health and Human Services asked the Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS) to assess the adequacy of information regarding analytic validity and clinical validity, and utility of genetic tests; the availability of proficiency testing (PT) for genetic tests; and communication aides to guide test selection and interpretation of results.

- The SACGHS used a broad interpretation of oversight that included federal and state governments and agencies, private-sector organizations, health professionals, payers, patients and consumers.
- Although the SACGHS was tasked to look at the oversight of genetic testing specifically, it found that the issues associated with genetic tests do not differ markedly from other complex laboratory tests (i.e., genetic tests are not unique or exceptional for oversight purposes).

Key players in the US oversight system for genetic testing

- Currently in the USA, there are two main pathways to make genetic tests available for clinical use: genetic tests are developed as products by *in vitro* diagnostic test manufacturers for commercial distribution to multiple laboratories, and laboratory-developed tests are made for use solely within the developer's laboratory and are not sold to other entities. The US FDA and the Centers for Medicare and Medicaid Services are the key federal agencies that regulate these pathways.

Key findings

- The SACGHS identified gaps in five main areas of the oversight for genetic testing:
  - Clinical laboratory quality assurance
  - The transparency of laboratory performance and the validity of genetic testing
  - The oversight of the clinical validity of genetic tests
  - The level of current knowledge regarding the clinical utility of genetic tests
  - Meeting the informational needs of health professionals, the public health community, patients and consumers.

SACGHS recommendations to enhance the oversight of genetic testing

- To improve clinical laboratory quality assurance, the Centers for Medicare and Medicaid Services should require PT of all nonwaived laboratory tests for which PT products are available.
- To enhance the transparency of laboratory tests, the US Department of Health and Human Services (HHS) should appoint and fund a lead agency to develop and maintain a mandatory, publicly available, web-based registry for laboratory tests.
- To help close the gaps in oversight related to clinical validity, which would help assure the appropriate use of laboratory tests, the FDA should assess all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test).
- To better understand the usefulness of genetic tests, the HHS should create and fund a public–private partnership to evaluate the clinical utility of genetic tests, develop a research agenda to address gaps in knowledge, and conduct public health surveillance to assess the health impact of genetic testing.
- To meet the varied informational needs of health professionals, public health workers, patients and consumers, the HHS should support efforts to identify education or training deficiencies in each of these groups and support research and development of effective clinical decision support systems.

Conclusion

- The SACGHS report highlights the complexity of the US oversight system and urges the coordination of activities associated with the oversight of genetic testing, including policy and resource development, education, regulation and knowledge generation.

The emergence of pharmacogenomic tests (see definition in Box 1) presents challenges to product labeling, which is the FDA's first line of communication for indicated uses, instructions and warnings. Traditional labeling may not be able to fulfill this role in the case of genetic tests that are used in conjunction with drugs or other biologic therapies. Clinicians need clear and timely instructions on how to target drugs, but there has been wide variation in this information in the drug/test products that the FDA has approved. For example, the HER2 test and Herceptin ™ are expressly cross-labeled for use together [111]; the drug label identifies specific tests and provides information on how to vary prescribing based on test results. For other drugs, labeling merely notes that patient response may vary based on genetic factors but provides no specific information regarding testing and interpretation of results [112]. In addition, even if a drug label includes pharmacogenomic information, this information does not indicate or guarantee that an FDA-reviewed genetic test is commercially available.

In the USA and abroad, EHRs are recognized as a tool to improve the quality and consistency of patient care [2,3]. EHRs and informatic applications will be critical in realizing the maximum benefit from genetic and genomic tests. The EHR is significantly more than an electronic replacement for patient charts and printed reports. It is an interactive system in which transactions, such as medication orders, can be evaluated using context-specific algorithms to assess whether a decision is appropriate for a particular patient. Computerized systems that capture and deliver genetic test results to the provider can help detect procedural errors in the laboratory and reduce communication errors between the laboratory and the provider. Although a number of hurdles needs to be addressed before EHRs are fully embraced, the adoption of EHR systems will help to ensure that genetic test results are appropriately, consistently and continuously utilized in the delivery of patient care.

As healthcare practices advance to embrace a personalized medicine paradigm, all sectors of the oversight system – federal and state regulatory agencies, industry, the healthcare community and consumers – will play pivotal roles in ensuring the optimal use of genetic testing.

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Table 1

Elements of the US regulatory oversight framework for genetic testing.

Area of jurisdiction	Element of oversight
Regulation of clinical laboratories and testing services	Federal: CLIA overseen by the CMS, with involvement of other federal agencies (e.g., the US FDA in categorization of tests and the FTC in oversight of advertizing) Some states: e.g., New York, Washington, California
Medical products	Federal: FDA regulation of genetic tests and therapies codeveloped with genetic tests; oversight of marketing shared between FDA and FTC
Coverage and reimbursement for genetic testing	Federal: CMS, ERISA for employer-provided self-insured plans [4] State: state health programs and insurance regulations affecting private insurers Informal/private sector: e.g., medical necessity and utilization review practices
Clinical practice (e.g., when, whom to test; physicians' claims and disclosures regarding tests)	State law: medical practice and pharmacy regulations, consent laws, genetic privacy acts, tort law Informal oversight: voluntary, evidence-based guidelines and standards produced by professional organizations and government agencies
Specific uses and misuses of test results (e.g., privacy and data security; discrimination in employment and insurance; torts involving inappropriate or mistaken uses of genetic information)	Federal: ERISA [4], Health Insurance Portability and Accountability Act [5], Americans with Disabilities Act [6] State: statutes and tort law

CLIA: Clinical Laboratory Improvement Amendments; CMS: Centers for Medicare and Medicaid Services; ERISA: Employee Retirement Income Security Act; FTC: Federal Trade Commission.

Data taken from [104].

Table 2

Summary of SACGHS oversight recommendations (Evaluation of Genomic Applications in Practice and prevention

Identified gap	Recommended actions
Clinical laboratory quality assurance	Require PT for all nonwaived laboratory tests for which PT products are available Promote development of reference materials and methods Augment training of CMS laboratory inspectors Strengthen CMS enforcement efforts
Transparency of testing	Develop and maintain a mandatory, publicly available, web registry for laboratory tests that provides information on test availability, analytical validity, clinical validity and, where available, clinical utility
Oversight of the clinical validity of genetic tests	Increase the US FDA's role in the oversight of test clinical validity Escalate the FDA's and FTC's monitoring and enforcement efforts against laboratories and companies that make false and misleading claims
Current knowledge regarding the clinical utility of genetic tests	Create and fund a public/private partnership to assess clinical utility Develop a research agenda to address gaps in knowledge Conduct public health surveillance to assess health outcomes and the impact of genetic testing
Informational needs of health professionals, the public health community, patients and consumers	Identify education and training deficiencies among health professionals, public health workers, patients and consumers Support development of effective educational and training resources such as clinical decision support systems Clarify the nature and scope of FDA's oversight of clinical decision support systems

CMS: Centers for Medicare and Medicaid Services; FTC: Federal Trade Commission; PT: Proficiency testing; SACGHS: Secretary's Advisory Committee on Genetics, Health and Society.